

Fig. 1.—Endometrial surface, showing size of tumor.

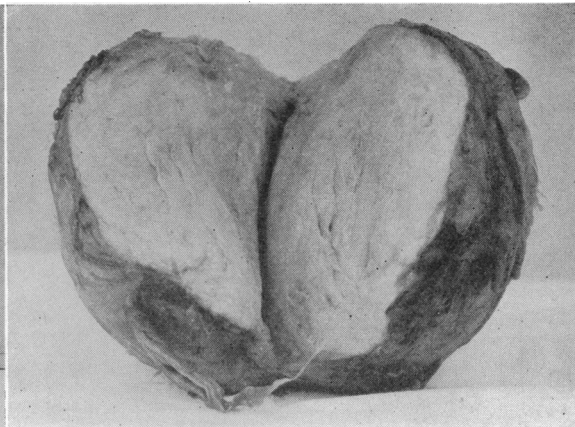


Fig. 2.—Cut section, showing extreme thinness of endometrial covering.

Postoperative course has been uneventful, except for three days of a pyelitic fever, associated with 70 white blood cells to the field in the catheterized specimen. This responded well to therapy, and the patient is now doing exceptionally well.

COMMENT

The accompanying figure amply illustrates the size and type of tumor removed. In consistency it is for the most part a fibroma, with a small amount of muscular tissue. The endometrium over the tumor was thinned out to almost tissue-paper thickness, but otherwise was entirely normal grossly. No microscopic section was done. Postoperative diagnosis: Fibromyoma uteri with hemorrhage; weight, 60 ounces.

1. This is one of those rare cases of fibromyoma uteri occurring in an individual less than twenty years of age.

2. It is also one in which the differential diagnosis between pregnancy and other tumors was difficult, it not impossible, at the time when first seen.

3. This type of tumor can develop with most amazing speed. Check-up of the patient's prior record reveals that not the faintest semblance of a tumor existed in August, 1936.

402 Walker Street.

REFERENCES

1. Anspach, B. M.: Gynecology, pp. 292 *et seq.*, 1924.
2. Norris, C. C.: Harper's Medical Monographs, pp. 112 *et seq.*, 1930.
3. Lynch, F. W.: Gynecology and Obstetrics. C. H. Davis, Chap. XII, Vol. 2.

ACRIFLAVINE AND LIVER DAMAGE WITH A REPORT OF A FATALITY ASSOCIATED WITH ITS USE

By O. C. MARSHALL, M.D.
Watsonville

RELATIVELY little is known concerning the effect of some of the commonly used urinary antiseptics upon certain organs of the body, especially the liver. It is only in the rare case coming to necropsy wherein urinary antiseptics have been extensively used, and in experimental work upon certain animals, that their action can be studied.

The purpose of this report is to summarize the available material in medical literature concerning acriflavine and its effects on the liver with a report of a case terminating fatally, evidently from its use. Further work is being done in the pathology department of Stanford Medical School upon the interesting effects of acriflavine upon the liver.

Acriflavine is one of a class of dyes used as a urinary antiseptic. It is most often prescribed as neutral acriflavine for systemic use and¹ recommended as enteric coated tablets of one-half grain each from three to eight tablets daily (96 to 256 milligrams). Also it is available for intravenous usage in doses of 100 to 500 milligrams, recommended to be dissolved in 20 to 50 cubic centimeters of normal saline and given daily for three days, and then every three to four days. Locally it is used commonly for urethral irrigations.

The action of living tissue indicates it to be a toxic dye. It readily stains the skin, such stain being removed with difficulty, and Heathcote and Urquhart² found that heart muscle absorbed and retained it in spite of prolonged perfusion with Ringers' solution. It was found to be depressing to certain tissues, a 1:1,000,000 solution depressing the heart, a 1:25,000 solution depressing intestinal muscle, and a 1:20,000 solution depressing skeletal muscle. Weaker solutions produced some stimulation of intestinal and skeletal musculature. The same investigators reported favorable bactericidal action on staphylococci, but found certain strains of gonococci quite resistant to acriflavine. Gilbrandsen³ found the minimum fatal dose for monkeys to be about 30 milligrams per kilogram, body weight, and it appeared to kill by depressing the heart.

Heathcote and Urquhart² made quite extensive studies upon the action of acriflavine upon dogs, using various-sized doses. They used the drug intravenously and intramuscularly and found: (1) a dose of 50 milligrams per kilo killed at once; (2) sublethal doses of 25 milligrams per

¹ "Catalog of Specialties" (Abbott).

² Heathcote, R. St. A., and Urquhart, A. L.: Pharmacological and Toxicological Actions of Acriflavine, *Pharmacol. and Exper. Therap.*, 38:145-160 (Feb.), 1930.

³ Gilbrandsen: *Proc., Roy. Soc. B*, 90:136, 1919.

kilo at two-day intervals caused death in two to four doses; and (3) repeated smaller doses (5 to 12 milligrams per kilo) by intravenous or intramuscular injections at two-day intervals caused death or produced serious liver damage within fifteen to sixty days.

In the case of sudden death by larger doses, the cause was apparently cardiac depression, and in those dying after a delayed period the cause was due to liver injury. Necropsy findings upon those dying within the first week were practically a uniform cloudy swelling of the liver parenchyma and kidney epithelium. Those found from seven to twenty-one days after the first dose of acriflavine showed, in addition to cloudy swelling, an atrophy of the liver parenchyma and kidney epithelium, with some focal necrosis and pigmentation of the spleen. Those dying or destroyed in the interval from the twenty-first to the sixtieth day showed, in addition to the atrophy of the liver and kidney cells, a uniformly common focal necrosis situated chiefly around the central veins of the liver lobules and a congestion of the liver sinuses. The kidney showed a tubular atrophy. The marked pigmentation of the spleen indicated destruction of erythrocytes. The intramuscular sites where injection of the drug was given showed abscess formation.

One feature of the animals surviving sufficiently long was the great degree of emaciation attributed to liver injury.

McKelvey Bell⁴ reported its use on persons by intravenous use and by enteroclysis. He considered it effective for many acute infections if used for one or two injections of a one-half per cent neutral acriflavine in 50 cubic centimeters volume at weekly intervals. He often noted alarming symptoms from it and warned against its frequent use.

Murray⁵ reported its application in 118 cases, mainly of gonorrhea in the British troops. He used five cubic centimeters of a two per cent solution (100 milligrams) twice weekly, ranging from five to twenty-six doses intravenously. He noted toxic symptoms, and attributed one death to its use as showing an acute yellow atrophy of the liver.

The toxic symptoms are apparently divided into immediate and delayed symptoms. Bell reported complaints of transient fainting, vomiting, palpitation of heart, and two cases of mild shock. Old people complained of several days of weakness, lassitude, and depression following a second dose. Women tolerated the dosage poorly. The people who received four to five injections appeared to develop a gastritis with epigastric pains, nausea, and albuminuria.

Murray noted marked delayed actions appearing after a lapse of eight or more weeks, wherein 11 per cent of all cases receiving acriflavine (doses of five cubic centimeters of a two per cent solution) developed a jaundice against an average

of 32 per cent in the untreated British troops. There was apparently no relationship between the number of doses administered and the occurrence of jaundice. Bell also noted a cardiac irritability developing about the fifteenth day. The fatal case reported by Murray presented similar but more marked symptoms than the others suffering from jaundice and, in addition to the icterus, showed loss of appetite and vomiting, slight pyrexia, bile-stained urine, paler stools, and tender liver at the costal margin. In the majority of cases the jaundice disappeared in ten days, and in a majority of cases the men recovered in thirty days. In the patient who died twenty days after hospital admission, diagnosis was acute yellow atrophy of the liver. This patient showed a leukopenia (1,400).

REPORT OF CASE

F. M., Age twenty-four years. American. Bank clerk.

Past History.—Never had any severe infections; only a mild specific urethral infection in 1927, which responded well to treatment, but which appeared to have become aggravated in October before the use of acriflavine. Past average weight was about 205 pounds (90½ kilos).

Present Illness.—Gave a history of taking six acriflavine tablets daily (192 milligrams) from October 25 to December 22, or a total dose of about 11.1 grams. Early in November he began having periods of malaise, and about the middle of the month developed stabbing epigastric pains, with loss of appetite. Weight loss of 14 to 17 pounds during December, and about the same during the illness in January. During December he became quite weak, and developed marked tenderness in the liver with a constant epigastric distress. About January 6 he became markedly lethargic, associated with insomnia, which persisted until two days before death, when he passed into coma and expired.

Physical Examination.—When first seen on January 8 he was lethargic, and movement of body caused abdominal pain. Jarring over the liver was quite painful. Temperature was normal, pulse 64. On January 9 he developed a jaundice which became increasingly worse until death on January 20. The urine progressively became darker and the stools lighter. Temperature became elevated on January 15 and reached 104.2 finally. Had some vomiting during illness. Abdomen became much distended on the 19th with an anuria. Pulse became increasingly fast and reached 140.

Laboratory Examination.—Urine contained albumin two plus, much bile and, apparently cystine crystals. Widal was negative. Blood count of 6,000 white blood cells.

Clinical Diagnosis.—Acute yellow atrophy of liver.

Autopsy Report.—(Half-hour after death.) Moderate jaundice, with distended tympanitic abdomen present. No edema noted. The abdomen contained about one-half to one quart of dark yellow fluid. The jejunum and duodenum were sprinkled with many hemorrhagic spots the size of pin-heads or larger. The liver was firm in consistency and was decreased about one-third in size. The left lobe and the central portions were more involved than the right. On section the liver showed many regularly distributed nodules or granules on a yellow-green surface. The spleen was moderate-sized and stained a yellow green. The kidneys were moderately enlarged and bile-stained. The heart was enlarged and flabby.

Histologic Examination.—Spleen: Intense congestion of the sinusoids. In places are focal areas of necrosis, in which are rather numerous mononuclear cells, many red cells, and polymorphonuclear leukocytes.

Liver: In large, poorly circumscribed areas corresponding in position to the central parts of the lobules, many liver cells are swollen to several times the normal size, and the cytoplasm of these cells contain many vacuoles, but the nuclei of most cells are intact. Surrounding these cell groups there is a moderate amount of cellular fibrosis tissue, which in places extends between degenerating cells,

⁴ Bell, McKelvey: M. J. and Rec., No. 5, Vol. 120, p. 437, 1934.

⁵ Murray, D. H.: Acriflavine: Its Use by Intravenous Injection in Treatment of Gonorrhea, J. Roy. Army M. Corps, 54:19-27 (Jan. 30), 1930.

and also extends into groups of otherwise normal appearing cells. There is a moderate irregular round cell and polymorphonuclear leukocytic infiltration of the fibrous tissue, which also contains large phagocytes filled with brown granular pigment. There are also a moderate number of proliferating bile ducts.

Kidney: Slight congestion and cloudy swelling. The glomerular tufts are normal, though some capsular spaces contain granular material. Many tubules contain small hyaline casts.

Diagnosis.—Cirrhosis of liver, subacute; splenitis, subacute.

COMMENT

This case apparently harmonizes with the clinical effects of acriflavine upon the liver as reported in the literature. Apparently there is an accumulation of the dye in the liver cells which may even produce a progressive injury to the liver parenchyma extending several months after the drug is discontinued. The action appears to be uniform in type, but variable in amount. There must be a large number of cases where injury was present without symptoms severe enough to attract clinical attention. It makes necessary a more critical examination of patients for liver injury, especially those receiving drugs similar to acriflavine in action.

IN CONCLUSION

1. The use of acriflavine systemically and continuously is attendant with dangers.
2. The drug is apparently readily absorbed from the intestinal tract and is retained by the liver cells for a considerable period of time.
3. Acriflavine exerts a decided immediate toxic action on the heart, and a delayed toxic reaction on the liver.
4. It produces a secondary loss of weight due to liver injury.
5. It causes destruction of erythrocytes and a leukopenia.
6. Experimental work is needed on similar drugs as related to liver injury.
7. The fatal case here reported indicates the desirability of enjoining caution on the indiscriminate use of acriflavine.

Register Building.

A SIMPLE ABDOMINAL CUP FOR CONTROLLING CYSTOTOMY DRAINAGE

By JOSEPH E. TILLOTSON, M.D.

Woodland

CYSTOTOMY wounds present practical and esthetic features that invariably require much attention on the part of the patient and all who have to do with their care. The writer has improvised a rather simple abdominal cup which eliminates many and minimizes other unfavorable features associated with a cystotomy.

The working apparatus, illustrated in Figure 1, comprises the following: A is a running-water aspirator. This is an economic and simple type, attachable to any shaped water faucet. Any suction apparatus, whether running-water type in design or motor-driven, will serve just as well. The bottle, B, is connected by tubing to the aspi-

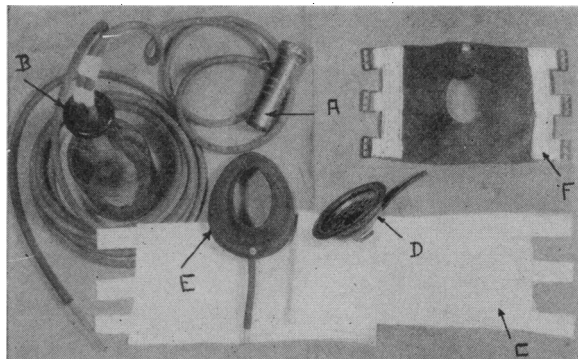


Fig. 1.—Working apparatus, illustrating component parts. A, running-water aspirator; B, bottle with rubber tubing for collecting urine; C, muslin abdominal binder; D, tin cups and copper tubing soldered together; E, pneumatic rubber rim, commonly used on conventional anesthetic inhalers; F, rubber mat, with buckles for attachment to abdominal binder.

rator, and further connected by tubing to reach the patient; it collects urine and other discharge from the bladder. The abdominal part of the apparatus is formed of C, D, E, and F. C is an abdominal binder, made of muslin to the exact size of the patient. Two or three are made so that they may be washed and changed daily. D, or the main part of the cup, is made from tin cake-cups fitted with copper tubing and all soldered together. E is a pneumatic rubber rim, commonly used on conventional anesthetic inhalers. F is a rubber mat that goes over the metal cup when the latter is encircled by the pneumatic rim and fitted with buckles for attachment to the muslin abdominal binder. This particular mat was made from a piece of automobile tire inner-tubing and fitted with buckles and straps—a procedure easily done in the sewing department of the usual hospital.

Figure 2 shows the apparatus set up, ready to apply to the patient. Figure 3 shows it fitting on the abdomen. The patient, when his general condition permits, may get in and out of bed with the apparatus attached, working and maintaining complete dryness.

The cup may be applied immediately following a cystotomy operation. Once a day, or oftener, the cup is removed and the gauze changed. In the early stage of a prostate operation, for instance, there may be considerable blood, mucus, and sometimes pus, which may obstruct the cup to a degree, so that occasional cleansing is desirable. After a

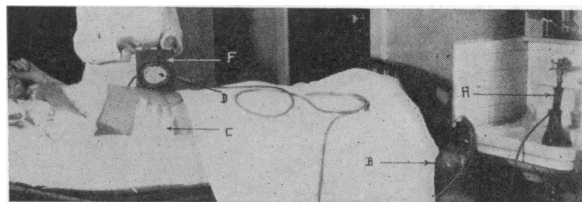


Fig. 2.—Apparatus set up ready to apply to patient. A, running-water aspirator attached to faucet; C, binder encircling body ready to be buckled to F, the rubber mat which steadies the cup, D. In the latter is a small fold of gauze which carries the urine from the surface of the abdomen near the wound to the upper compartment in the cup, where the fluid is aspirated away and collected in the bottle, B.